IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

FOREST LABORATORIES, INC., et al., Plaintiffs, v. COBALT LABORATORIES INC., et al., Defendants.	C.A. No. 08-021 (GMS) (LPS) CONSOLIDATED
FOREST LABORATORIES, INC., et al., Plaintiffs, v. BARR LABORATORIES, INC., et al., Defendants.	C.A. No. 08-022 (GMS) (LPS)
FOREST LABORATORIES, INC., et al., Plaintiffs, v. DR. REDDY'S LABORATORIES, INC., et al., Defendants.	C.A. No. 08-052 (GMS) (LPS)
FOREST LABORATORIES, INC., et al., Plaintiffs, v. ORGENUS PHARMA INC., Defendant.	C.A. No. 08-291 (GMS) (LPS)

FOREST LABORATORIES, INC., et al.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 08-336 (GMS) (LPS)
APOTEX INC., et al.,	)	
Defendants.	)	

PLAINTIFFS' REPLY BRIEF IN FURTHER SUPPORT OF THEIR CONTINGENT CROSS-MOTION TO TRANSFER

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I. INTRODUCTION

Orchid India's argument that ***all*** claims against ***all*** Defendants must be transferred to the District of New Jersey, or none of the claims may be transferred, is meritless. The controlling authority provides that this Court may sever Plaintiffs' claims against Orchid India and transfer them to a different district, while the other twenty-two Defendants who have not contested personal jurisdiction remain in this District.

Should this Court decline to exercise jurisdiction over Orchid India, severance and transfer of Plaintiffs' claims against Orchid India to the District of New Jersey is appropriate. Orchid India has not previously contested jurisdiction there, and has repeatedly stated that New Jersey would be an appropriate forum.

Severance and transfer of Plaintiffs' claims would also serve the interests of justice. Orchid India steadfastly ignored Plaintiffs' inquiries regarding Orchid India's designated agent for service in the United States – information that Orchid India is required by federal regulation to provide. As a result of Orchid India's refusal to provide this basic information, Plaintiffs had to conduct their own good faith investigation and reasonably believed (and still do) that this District is an appropriate forum in which to sue Orchid India.

But the possible jackpot that could result from Orchid India's jurisdictional gamesmanship has given it every incentive to fight severance and transfer to New Jersey. If the case against Orchid India were dismissed, rather than severed and transferred, Orchid India would likely argue that it is no longer subject to the automatic stay of FDA approval of its ANDA for a generic version of Plaintiffs' NAMENDA® product. If this were so, Orchid India would be able to proceed with an at-risk launch of its generic product – well ahead of the expiration of the statutorily-mandated stay. An at-risk launch would force Plaintiffs to engage in premature preliminary injunction proceedings to protect their patent rights, and potentially cost

them hundreds of millions of dollars in lost revenues. Moreover, the other twenty-two Defendants would be penalized for playing by the rules. These remaining Defendants would remain unable to launch their own generic versions of NAMENDA®, as they would still be subject to the automatic stay of FDA approval on their respective ANDAs.

Orchid India's blatant attempt to manipulate the Hatch-Waxman statutory scheme should not be permitted. Accordingly, if this Court declines to exercise jurisdiction over Orchid India, Plaintiffs respectfully request that Plaintiffs' contingent motion to transfer be granted.

II. ARGUMENT

As discussed in Plaintiffs' opening brief (D.I. 100 at 31-33), a district court may transfer a civil action to any other district if (1) the claims could have been brought in the transferee district in the first place, and (2) transfer is in the interest of justice. *See* 28 U.S.C. § 1406(a). Orchid India has failed to refute Plaintiffs' showing that these two requirements are readily satisfied in this case.

A. Transfer Is Appropriate Because Orchid India Could Have Been Sued In The District Of New Jersey

The first requirement of § 1406(a) – that the claims could have been brought in the transferee district – is satisfied here, because Orchid India is plainly subject to personal jurisdiction in the District of New Jersey. (D.I. 100 at 33.) Indeed, in its motion to dismiss, Orchid India has argued that New Jersey would have been a proper venue for Plaintiffs' claims against it. (D.I. 44 at 4-5 n.2.) Even now, in its opposition to Plaintiffs' contingent motion to transfer, Orchid India does not contest that it is subject to personal jurisdiction in New Jersey, or that it would have been at the time Plaintiffs filed their Complaint.[1] Instead, Orchid India states

[1] Orchid India's assertion that Plaintiffs "have not even attempted to address the [jurisdictional] requirement" of § 1406(a) (D.I. 133 at 25) is wrong. Plaintiffs made clear in

that "New Jersey, rather than Delaware, is a more convenient forum for the parties." (D.I. 133 at 24.) Orchid India has also not contested personal jurisdiction in four other cases in the District of New Jersey in which it has been named as a Defendant.[2]

Orchid India's sole argument with regard to the first requirement of § 1406(a) is that the ***entire case*** against ***all Defendants*** must be transferred to the District of New Jersey, should the claims against Orchid India be transferred. (D.I. 133 at 25-26.) This argument makes no sense,[3] and finds no support in the controlling legal authority.

1. **Orchid India Misconstrues The Plain Language Of § 1406(a)**

Orchid India contends that the "plain language of § 1406(a) mandates proof that the entire 'case . . . could have been brought' in that district, such that the entire 'case' may be transferred." (D.I. 133 at 25.) But the actual language of the statute contains no such requirement. Instead, § 1406(a) provides that a "district court of a district in which is filed a case laying venue in the wrong division or district shall dismiss, or if it be in the interest of justice, ***transfer such case*** to any district or division in which it could have been brought." 28 U.S.C. § 1406(a) (emphasis added). The word "entire" is nowhere to be found in § 1406(a), and Orchid

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their opening brief that Orchid India is subject to jurisdiction in the District of New Jersey. (D.I. 100 at 33.)

[2] *See Hoffmann-La Rouche Inc. v. Orchid Chems. & Pharms., Ltd.*, 2:07-cv-4582 (D.N.J.) (Chesler, J.); *Sepracor Inc. v. Sun Pharm. Indus. Ltd.*, 3:07-cv-4213 (D.N.J.) (Cooper, J.) (consolidated 3:07-cv-4623); *In re Desloratadine Patent Litig.*, 3:07-cv-3930 (D.N.J.) (Cooper, J.) (consolidated 3:06-cv-4715 in MDL); *Cima Labs, Inc. v. Orchid Chems. & Pharms., Ltd.*, 2:06-cv-4809 (D.N.J.) (Hayden, J.).

[3] This case involves twenty-three Defendants from across the United States and around the world. (*See* D.I. 100 at 20.) All of these Defendants, save Orchid India and its wholly-owned subsidiary, have consented to jurisdiction in the District of Delaware. If these Defendants were all transferred to the District of New Jersey, as Orchid India suggests, there is a significant chance that some of them would move to dismiss for lack of personal jurisdiction and be transferred back to the District of Delaware. This game of jurisdictional ping-pong would be a waste of judicial resources and is plainly not the result contemplated by § 1406(a).

India's transparent attempt to alter the plain language of the statute and read an "entire case" requirement into § 1406(a) must fail.

2. Orchid India Misinterprets The Relevant Caselaw And Ignores Contrary Precedent

Orchid India's self-serving attempt to read the word "entire" into the transfer requirements of § 1406(a) is also unsupported by the relevant caselaw. Contrary to Orchid India's assertion (D.I. 133 at 25-26), that statute does not mandate that an entire case against all defendants be transferred if venue is not proper as to one of them. Cases that interpret § 1406(a) have found just the opposite – although a district court ***may*** transfer an entire case to another district, such a transfer is by no means mandatory.

The Third Circuit has emphasized that a district court can sever claims against a given defendant for purposes of transfer:

> In the situation where venue is proper for one defendant but not for another and dismissal is inappropriate, ***the district court has a choice***. One option is to transfer the entire case to another district that is proper for both defendants. ***Another alternative is to sever the claims***, retaining jurisdiction over one defendant and transferring the case as to the other defendant to an appropriate district.

Cottman Transmission Sys., Inc. v. Martino, 36 F.3d 291, 296 (3d Cir. 1994) (emphasis added); *see also Rappoport v. Steven Spielberg, Inc.*, 16 F. Supp. 2d 481, 496 (D.N.J. 1998) ("In situations where the claims against one or more defendants are severed because of improper venue, a district court may then transfer the severed claims to another district pursuant to § 1404(a) or § 1406(a)."). It is precisely such severance and transfer that Plaintiffs seek here, in the event that the Court declines to exercise personal jurisdiction over Orchid India.

In support of its argument, Orchid India relies on a single, unpublished decision from the Western District of Wisconsin, *Wild v. Heart of Texas Dodge, Inc.*[4] (D.I. 133 at 26.) Orchid India misinterprets *Wild* to mean that § 1406(a) "***mandates***" that all defendants in a case must be transferred together, even if (as here) plaintiffs do not seek to transfer all defendants. (D.I. 133 at 25.) In fact, *Wild* stands for the uncontroversial proposition that, ***when a plaintiff seeks to transfer all defendants***, a district court must determine whether all defendants are subject to jurisdiction in the transferee forum.[5] *Wild* is clearly inapposite to the facts in this case, leaving Orchid India without any support for its strained interpretation of § 1406(a).[6]

Orchid India's attempts to distinguish *FS Photo* and *Stein* (D.I. 100 at 31) are similarly unavailing. According to Orchid India, the question before this Court in *FS Photo* and *Stein* "was whether to dismiss or transfer based on venue, after determining it had personal jurisdiction." (D.I. 133 at 27 n.8.) But this is a distinction without a difference. As this Court previously noted in another case upon which Orchid India relies (*id.* at 26, 30), the U.S. Supreme Court has held "that § 1406(a) is not limited to cases in which the transferring court has personal jurisdiction over the defendants." *See Athletes Foot of Del., Inc. v. Ralph Libonati Co., Inc.*, 445

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[4] No. 01-C-0461-C, 01-C-0463-C, 2001 WL 1913400 (W.D. Wis. Nov. 23, 2001).

[5] In *Wild*, plaintiffs sought to transfer their two cases against multiple defendants back to the Eastern District of Louisiana – the same district that had previously transferred the cases to the Western District of Wisconsin. *Wild*, 2001 WL 1913400, at *2. As plaintiffs affirmatively sought to re-transfer each and every defendant to Louisiana, plaintiffs were required to show that "***all*** of the defendants would be subject to the [transferee] court's jurisdiction." *Id.* (emphasis added). However, because not all defendants resided in that forum, transfer of ***all*** defendants (as the *Wild* plaintiffs specifically sought) was not permissible. *Id.* at *3. The Court also noted that "transfer decisions are interlocutory decisions and therefore not subject to review." *Id.*

[6] The district court's analysis in *Wild*, moreover, supports ***Plaintiffs'*** contingent motion to transfer. In *Wild*, the district court determined that one of the transferred defendants was not subject to jurisdiction in Wisconsin, and thus "[a]t the very least" the district court in Louisiana "should have ***severed*** this defendant from the rest of the case and retained jurisdiction." *Wild*, 2001 WL 1913400, at *3 (emphasis added).

F. Supp. 35, 49 n.47 (D. Del. 1977) (citing *Goldlawr, Inc. v. Heiman*, 369 U.S. 463, 466-67 (1962)); *see also Scott Paper Co. v. Nice-Pak Prods., Inc.*, 678 F. Supp. 1086, 1090 (D. Del. 1988) (observing that the court "need not make a determination that it has personal jurisdiction over the defendant in order to transfer the case under § 1406(a)," and transferring the matter to the Southern District of New York). There is no question that this Court need not exercise jurisdiction over Orchid India in order to sever and transfer Plaintiffs' claims against it pursuant to § 1406(a), and Orchid India's suggestion to the contrary is incorrect.

B. Allowing Orchid India To Profit From Its Jurisdictional Gamesmanship Would Be Contrary To The Interests Of Justice

Denial of Plaintiffs' contingent motion to transfer would serve only the selfish "interests" of Orchid India – ***not*** of justice. If this Court finds that it cannot exercise personal jurisdiction over Orchid India, it would serve the interest of justice to sever and transfer Plaintiffs' action against Orchid India to the District of New Jersey.

Contrary to Orchid India's suggestion, Plaintiffs' decision to sue Orchid India in the District of Delaware was not the product of bad faith. (*See* D.I. 133 at 26-30.) Instead, it was a result of Orchid India's self-serving game of "hide the ball." But notably, the United States Supreme Court has found that § 1406(a) was enacted precisely to prevent the existence of an "elusive fact" from leading to dismissal of an entire case:

> The ***problem which gave rise to the enactment of [§ 1406(a)] was that of avoiding the injustice which had often resulted to plaintiffs from dismissal of their actions merely because they had made an erroneous guess with regard to the existence of some elusive fact*** of the kind upon which venue provisions often turn. . . . ***The language and history of § 1406(a)***, both as originally enacted and as amended in 1949, ***show a congressional purpose to provide as effective a remedy as possible to avoid precisely this sort of injustice.***

See Goldlawr, 369 U.S. at 466 (citations omitted) (emphasis added).

1. Orchid India Steadfastly Refused To Identify A U.S. Regulatory Agent

Orchid India boldly asserts that Plaintiffs' decision to sue Orchid India in Delaware "was a conscious gambit to seek jurisdiction in an improper forum." (D.I. 133 at 29.) But the facts underlying Orchid India's own jurisdictional games tell a different story. (*See* D.I. 100 at 32-33.)

As stated in Plaintiffs' opening brief (D.I. 100 at 32-33), Orchid India notified Plaintiffs of its ANDA filing on December 7, 2007. (*See* Orchid India Notice Letter, Ex. 32.) Contrary to the requirements of 21 C.F.R. § 314.95(c)(7),[7] however, Orchid India's Paragraph IV notice letter was silent as to its U.S. regulatory agent for service – and Plaintiffs had only 45 days to determine who this agent was. *See* 21 U.S.C. § 355(j)(5)(B)(iii).

Plaintiffs were diligent in trying to discern this information. On January 4, 2008, Plaintiffs' counsel wrote to Dr. Billa Reddy, Orchid India's head of Pharma Research, in response to Orchid India's statutorily-mandated offer of confidential access to its ANDA. (*See* 1/4/08 Letter from A. Sawicki, Ex. 33.) As jurisdictional discovery has subsequently demonstrated, access to Orchid India's ANDA would have provided Plaintiffs with the identity of Orchid India's U.S. filing agent. However, counsel for Plaintiffs received no response to his January 4th letter.

Plaintiffs subsequently brought suit against Orchid India in Delaware, based upon their own investigation of the relevant jurisdictional facts. These facts included (D.I. 100 at 9):

- The presence in Delaware of Orchid India's wholly-owned subsidiary, Orchid Pharmaceuticals, Inc. ("Orchid Pharma");

[7] Pursuant to § 314.95(c)(7), a notice letter must include the name and address of a U.S. regulatory agent authorized to accept service of process for the applicant, if the applicant (1) does not reside in the United States, ***or*** (2) does not have a place of business in the United States. As discussed *infra*, both of these preconditions apply to Orchid India.

- Orchid India's representations to the public that it formed Orchid Pharma "to cater to the more demanding requirements of business development and logistical coordination in the US"; and

- Orchid India's representations to the public that Orchid Pharma was Orchid India's "agent for filing of regulatory submissions with the US FDA."

Even after the filing of their Complaint, Plaintiffs contacted Orchid India's litigation counsel and repeatedly requested the identity of the U.S. agent designated to accept service on Orchid India's behalf. (*See* 1/31/08 E-mail Correspondence, Ex. 34.) Orchid India steadfastly refused to provide that information. (*See id.*) In fact, Orchid India's trial counsel stated that he did not know who Orchid India would even designate:

> ***I am not aware of any need for [Orchid India] to appoint such an agent, nor whom they would designate if they were to conclude that one was appropriate.*** I could ask them, but in addition to being contrary to how others have treated the issue, what would be the point given [Orchid India's trial counsel's] willingness to accept service of this particular complaint? In any event, it is the middle of the night in India, and I would not get an answer today.

(*Id.* (emphasis added).) Not only did Orchid India's counsel fail to provide this information the next day, he failed to provide it at all.[8]

In spite of its own repeated stonewalling, Orchid India asserts that Plaintiffs' decision to sue Orchid India in Delaware was "not the product of a 'good faith' and mistaken belief." (D.I. 133 at 29.) For example, Orchid India now argues that it is "register[ed] to do business in New Jersey," and Plaintiffs thus should have known to sue them there. (*Id.* at 27.) But registration to do business in New Jersey does not mean that Orchid India has an actual place of business in the United States, or that its U.S regulatory agent is there. Similarly, Orchid India now contends that

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[8] Orchid India's assertion that "both Plaintiffs' counsel well knew that Orgenus was the entity assisting Orchid India in filing ANDAs (like ANDA No. 90-044) with the FDA" (D.I. 133 at 29) is wrong. Any possible awareness of Orgenus by Plaintiffs' counsel (or their respective law firms) during their representation of ***unrelated*** parties in ***unrelated*** cases has no bearing on this case.

an unrelated drop-box corporation, Corporation Service Company, is its registered agent in the United States, and that Orchid India's website lists Orgenus as a "Primary Business Contact for U.S. and Canada." (*Id.*) But regardless of whether these statements are true, the fact remains that Orchid India failed to identify ***any*** registered U.S. agent in its notice letter to Plaintiffs, as required by § 314.95(c)(7), and represented to the public that Orchid Pharma was its agent for filing regulatory submissions with the FDA. Orchid India apparently believes that it can dodge regulations in place in the United States, while at the same time force prospective plaintiffs to "guess" in which district court it would be amenable to suit.[9] This Court should not condone such tactics.

2. Dismissal Of This Case Would Prejudice Plaintiffs And The Remaining Defendants

Orchid India now seeks to gain an unfair advantage from its cultivated ignorance – but the motivation behind Orchid India's game-playing is readily apparent. Plaintiffs complied with the requirements of the Hatch-Waxman Act and brought their patent infringement claims against Orchid India in a forum that Plaintiffs believe could exercise jurisdiction over it. (*See generally* D.I. 100.) Approval of Orchid India's ANDA was then stayed, in accordance with the statutory scheme. But if this case is dismissed, Orchid India will likely argue that this stay could be lifted. (*Id.* at 31-32.) Orchid India could then attempt to launch (at risk) a generic version of Plaintiffs' NAMENDA® product well before the time contemplated by the Hatch-Waxman Act – a result that would severally prejudice and irreparably harm Plaintiffs and the other twenty-two

[9] Orchid India's suggestion that Plaintiffs should be faulted for not filing a "protective suit" in the District of New Jersey is disingenuous. (*See* D.I. 133 at 29-30.) Plaintiffs filed protective suits against other defendants in this action based on the agents properly identified by those Defendants in their respective notice letters or during subsequent communications within the 45-day deadline for suit. Had Orchid India complied with the FDA's regulations or responded to Plaintiffs' reasonable requests for information within that time frame, Plaintiffs may well have filed a protective suit against Orchid India.

Defendants in this action.[10] (*Id.* at 31-32.) Orchid India cannot be permitted to use its earlier non-compliance with the FDA regulations as a springboard to undercut the entire purpose of the Hatch-Waxman Act.

Plaintiffs would clearly be prejudiced if Orchid India were permitted to launch generic NAMENDA® at risk. Plaintiffs would be forced to engage in costly and time-consuming preliminary injunction proceedings, seek a temporary restraining order, and potentially lose hundreds of millions of dollars in revenue. And although Orchid India may arguably not be precluded from moving forward with their launch of generic NAMENDA®, all other Defendants would remain prohibited from doing so, due to the ongoing stay on FDA approval of their respective ANDAs.

Orchid India concedes as much, but argues that somehow its dismissal from this case would still be "in the interest of justice." (D.I. 133 at 30 & n.12.) As the only Defendant to fail to comply with § 314.95(c)(7), however, Orchid India should not be allowed to exploit the other Defendants' ***compliance*** with the mandatory FDA requirements, while wrapping itself in some supposed interest of justice. Although dismissing Orchid India from this action would undoubtedly place Orchid India ahead of the pack, the interests of justice weigh strongly against doing so.

III. CONCLUSION

Plaintiffs respectfully request that their Contingent Motion to Transfer (D.I. 99) be granted, should this Court decline to exercise jurisdiction over Orchid India.

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[10] This Court's decision in *Athletes Foot* is easily distinguishable. In that case, the Court noted that dismissal was appropriate, in part, because the statute of limitations had not run on plaintiff's claim. *Athletes Foot*, 445 F. Supp. at 49 n.47. Here, however, even Orchid India agrees that dismissal of Plaintiffs' claims arguably could result in "the expiration of the statutorily-mandated stay." (D.I. 133 at 30 n.12.)

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Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

December 07, 2007

CERTIFIED
Via ~~Registered~~ Mail
Return Receipt Requested

Howard Solomon
Chairman & and CEO
Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022

Merz Pharma GmbH & Co. KGaA
C/o G. Patrick Sage
Hueschen & Sage, PLLC
Kalamazoo Building, Seventh Floor
107 West Michigan Avenue
Kalamazoo, MI 49007

Dr. Martin Zugel
Merz Pharma GmbH & Co. KGaA
Eckenheimer Landstrasse 100
D-60318 Frankfurt am Main
Germany

Re: Memantine Hydrochloride Tablets, 5 mg and 10 mg.
Paragraph IV Certification for U.S. Pat. 5,061,703.

Dear Sirs:

Orchid Healthcare, a Division of Orchid Chemicals & Pharmaceuticals Ltd. ("Orchid"), is providing the following information pursuant to § 505(j)(2)(B)(ii) of the Federal Food, Drug, and Cosmetic Act ("the Act"):

1. In order to obtain approval to engage in the commercial manufacture, use, or sale of a certain Memantine product, Orchid,

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submitted to the Food and Drug Administration ("FDA") an Abbreviated New Drug Application ("ANDA") under § 505(j) of the Act that contains the required bioavailability or bioequivalence data or information. The FDA has documented the receipt of this application and has notified Orchid accordingly.

2. The ANDA number is 90-044.

3. The established name for the Memantine product is Memantine Hydrochloride Tablets, 5 mg and 10mg. Forest Labs markets Memantine Hydrochloride tablets, 5 mg and 10 mg under the brand name Namenda®.

4. The active ingredient, strength, and dosage form of the proposed drug product is Memantine Hydrochloride, 5 mg and 10 mg tablets.

5. The ANDA indicates that Orchid intends to market the Memantine product before the expiration date of U.S. Pat. No. 5,061,703 (the '703 patent). This patent is listed by the FDA in the Orange Book.

6. The ANDA indicates that the claims of the '703 patent are invalid and/or will not be infringed by the commercial manufacture, use, or sale of the Memantine product. Below is a detailed statement of the factual and legal bases for Orchid's conclusions. This information is supplied for the sole purpose of complying with the above-referenced statutes. Accordingly, Orchid does not waive any attorney-client privilege or work product immunity concerning the subject matter of this communication.

I. SUMMARY

Orchid's proposed memantine product will not infringe any claims of the '703 patent when properly construed. In addition, the claims of the '703 patent are invalid over the prior art, as well as under 35 U.S.C. § 101/112.

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The '703 patent indicates that:

> Cerebral ischemia is characterized by a pathophysiological situation defined by an imbalance of neuronal stimulation mechanisms. In this context, the excessive inflow of calcium through NMDA receptor channels finally leads to the destruction of brain cells in specific brain areas (Rothmann & Olney, Trends Neurosci 10, 1989, pp. 299).
>
> Therefore, in order to treat or eliminate this pathological situation, an antagonistic intervention is required with regard to the NMDA receptor channels (Kemp et al., Trends Pharmacol, Sci. 8, 1987, pp. 414).

Col 2, ln 46-56.

The '703 patent recites that "The present invention is aimed at ... employing compounds ... exhibiting an NMDA receptor channel-antagonistic and anticonvulsive action, for use in the prevention and treatment of cerebral ischemia." Col 2, ln 67-col 3, ln 3. The '703 patent further states that "[t]his objective can be achieved according to the invention by using the 1-amino adamantanes of formula (I)." Col 3, ln 4-6.

The '703 patent asserts that the use of the claimed compounds prevents an impairment or further impairment – *i.e.*, degeneration and loss of nerve cells – following ischemia. Therefore, the recited compounds allegedly are especially suited for the prevention and treatment of cerebral ischemia after apoplexy, open-heart surgery, cardiac standstill, subarachnoidal hemorrhage, transient cerebro-ischemic attacks, perinatal

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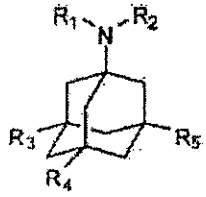
II. THE '703 PATENT

The '703 patent issued October 29, 1991 from an application filed April 11, 1990. The '703 patent claims priority to European patent application No. 89106657, filed April 14, 1989. An *ex parte* reexamination request was filed on August 18, 2004. The '703 patent reissued with amended and additional claims on November 7, 2006.

The '703 patent is listed in the U.S. Food and Drug Administration's Orange Book for Namenda®, which contains memantine as the active ingredient.

A. The Specification

The '703 patent indicates that it is directed to methods for the prevention and treatment of cerebral ischemia using an adamantane derivative of the formula



wherein R_1 and R_2 are identical or different, representing hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms; wherein R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl; and wherein R_5 is hydrogen or a straight or branched C_1-C_6 alkyl group. *See* '703 patent Abstract.

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asphyxia, anoxia, hypoglycemia, apnoea and Alzheimer's disease. The amount employed is a cerebral ischemia-alleviating or preventive amount. Col 3, ln 6-17.

The purported efficacy of the recited compounds with respect to antagonistic intervention in NMDA receptor channels is described in a series of in vitro and in vivo experiments that are detailed in the specification. Col 4, ln 55 – col 7, ln 59.

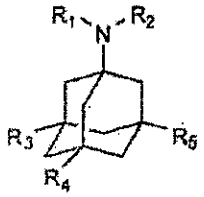
The specification concludes with various examples showing pharmaceutical compositions and methods for synthesizing different adamantane derivatives. Cols. 7 – 13.

B. <u>The Claims</u>

Initially Issued Claims

The '703 patent initially issued with 13 claims. Claim 1, then the only independent claim, is reproduced below

> 1. A method for the prevention or treatment of cerebral ischemia comprising the step of administering, to a patient in need thereof, an effective amount of an adamantane derivative of the general formula



> wherein
>
> R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

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wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein R5 is hydrogen or a straight or branched C1 -C6 alkyl group,

or a pharmaceutically-acceptable salt thereof.

Dependent claims 2-9 describe various substituents for R_1-R_5. Dependent claims 10-13 are reproduced below.

10. A method according to claim 1 for the treatment of Alzheimer's disease.

11. A method of claim 1, wherein the adamantane derivative is administered in an effective cerebral ischemia-alleviating or preventive amount.

12. A method of claim 11, wherein the adamantane derivative is administered in the form of a composition containing the same together with a pharmaceutically-acceptable carrier or diluent.

13. A method of claim 11, wherein the adamantane derivative is administered in an amount effective to prevent degeneration and loss of nerve cells after ischemia.

Claims Issued After Reexamination

The '703 patent, after reexamination, contains nineteen claims, three of which are independent. Claims 1, 10, 14, and 17 are reproduced below. The language added during reexamination is italicized.

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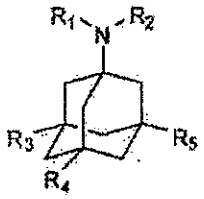
1. A method for the prevention or treatment of cerebral ischemia comprising the step of *orally* administering, to a patient *diagnosed with Alzheimer's disease and* in need thereof, an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1 -C_6 alkyl group, *and*

wherein

R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously;

or a pharmaceutically-acceptable salt thereof.

10. A method according to claim 1 for the treatment of Alzheimer's disease *wherein said adamantine derivative is memantine and said effective amount is from about 0.01 to 100 mg/kg.*

14. A method for the prevention or treatment of cerebral ischemia comprising orally administering to a patient diagnosed with Alzheimer's

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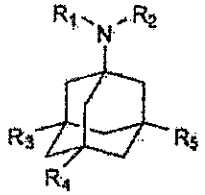
disease and in need of such treatment an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1 -C_6 alkyl group, and

wherein

R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously;

or a pharmaceutically-acceptable salt thereof.

17. A method for the treatment of an imbalance of neuronal stimulation after Alzheimer's disease, comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula

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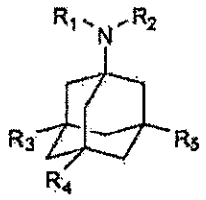

wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1 -C_6 alkyl group, and

wherein

R_1 R_3 R_5, R_4, and R_5 do not all represent hydrogen simultaneously

or a pharmaceutically-acceptable salt thereof.

C. The Prosecution History

The following is not an exhaustive summary of the prosecution history of the '703 patent from the earliest filing (*i.e.* from the filing of European Application No. 89106657 filed on April 14, 1989), including reissue proceedings initiated on August 18, 2004. Rather, it is limited to a summation of certain portions of the prosecution history.

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The Initial U.S. Application

The application resulting in the initial '703 patent was filed on April 11, 1990. The application was filed with 13 claims that were, with the exception of claim 10, allowed without amendment. Claim 10, as filed, is reproduced below.

> 10. A method according to claim 1 for the prevention or treatment of Alzheimer's disease.

On January 15, 1991, the Patent Office issued an Office Action allowing claims 1-9 and 11-13, but rejecting claim 10 under §§ 101 and 112 as not enabled—as the Examiner found no support for the claim that the designated compounds "prevent Alzheimer's disease." *Office Action, Jan. 15, 1991 at 2.* Claim 10 was also rejected under § 103 as unpatentable over European Application 0227410, which disclosed that "adamantane derivatives may be used to treat Alzheimer's disease and Alzheimer dementia." *Id.* at 3.

In response, the applicants amended claim 10 by deleting the words "prevention or" from the claim to limit the claim to "treatment" of Alzheimer's disease. *Amendment, February 7, 1991*, at 1. The applicants also argued that EP 0227410 did not suggest that the adamantyl group was "anything like a critical substituent in the complex compounds suggested by the reference for the treatment of Alzheimer's disease or Alzheimer dementia." *Id.* at 2. Therefore, the applicants asserted, there is nothing in the reference which indicates that the adamantyl group "has anything to do with the effectiveness of the compounds claimed ... to be useful in the treatment of Alzheimer's disease or Alzheimer dementia." *Id* at 2.

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On March 29, 1991, the Patent Office issued a Final Office Action allowing claims 1-9 and 11-13, and rejecting claim 10. The Examiner noted that no agreement had been reached regarding claim 10 during a telephonic interview. In particular, the examiner found there was "insufficient exemplary support for 'treatment of Alzheimer's disease.'"

The applicants filed a Request for Reconsideration and Withdrawal of Finality of the Final Rejection, noting that the Final Office Action contained a new basis for rejecting claim 10. In particular, the applicants noted that the Examiner initially rejected claim 10 for being directed to the prevention of Alzheimer's disease, whereas the subsequent rejection focused on the treatment of Alzheimer's disease being incredible *Request, May 20, 1991* at 1.

In response to the applicant's request for withdrawal of finality of the final rejection, the Examiner issued a Notice of Allowability of claims 1 through 13 on May 29, 1991. The '703 patent issued on October 29, 1991. On December 16, 1991, applicants filed a Request for Entry of Correction for certain typographical errors.

Request For Extension Of Patent Term—The '703 Patent

On December 9, 2003, Forest Laboratories – which is both the exclusive licensee of the '703 patent and the NDA holder for Namenda® – filed a Request for Extension of Patent Term under 35 U.S.C. § 156 for the '703 patent. Forest Labs indicated that memantine was approved by FDA on October 16, 2003 for the treatment of moderate to severe dementia of the Alzheimer's type. *Request for Patent Term Extension* at 2, 3. Forest Labs also asserted that claim 10 of the '703 patent "is explicitly directed to treatment of Alzheimer's disease, a method for using the approved product, NAMENDA™ (memantine hydrochloride), referring to claim 1 for the generic formula

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which included the approved active ingredient as explained infra. Claim 1 also covers a method of using the approved product in a generic manner." *Id.* at 5-6. Forest Labs also asserted that claims 2, 3, 6, 8, and 11-13 "cover a method for using" memantine. *Id.* at 6.

On December 27, 2006, Forest filed a Supplement to Request for Extension of Patent Term. The applicants noted that the '703 patent was reexamined by the Patent Office and as a result of the reexamination proceedings claims 1 and 10 were amended and claims 14-19 were added. *Supplemental Request for Patent Term Extension* at 1. The applicants asserted that "[a]ll information previously provided ... remains accurate. In particular, the '703 patent continues to claim a method of using [memantine], which is approved for the treatment of moderate to severe dementia of the Alzheimer's type, because claim 10 remains explicitly directed to the treatment of Alzheimer's disease and refers to independent claim 1 for the generic formula that continues to encompass memantine...." *Id.* at 2.

Request For Extension Of Patent Term—The '560 Patent

Also on December 9, 2003, Forest filed a Request for Extension of Patent Term under 35 U.S.C. § 156 for U.S. Patent No. 5,614,560.[1] In that petition, Forest again noted that memantine was approved for the treatment of moderate to severe dementia of the Alzheimer's type. *Request for Patent Term Extension* at 2. Forest Labs also asserted that "Claim 17 of the '560 patent depends from claim 1 and is specifically directed to a method of using the approved product, NAMENDA™ (memantine hydrochloride), for reducing neuronal degeneration in a mammal subject to a long-term non-ischemic

[1] The '560 patent issued March 25, 1997 from an application filed April 11, 1995. The '560 patent claims priority to an application filed on April 4, 1991. The claims of the '560 patent are directed to a method for reducing non-ischemic NMDA receptor-mediated neuronal degeneration in a mammal by administering memantine

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neurodegenerative disease, such as Alzheimer's disease (see '560 patent: col 3, lines 25-31). Claim 1 also covers a method of using the approved product in a generic manner." *Id.* at 5-6. Forest Labs also indicated that claims 2 and 4-8 "cover a method for using" memantine. *Id.* at 6.

The Reissue Application—The '703 Patent

The owner of the '703 patent filed a request for *ex parte* reexamination on August 18, 2004, on the grounds that a substantial new question of patentability might be deemed to exist under §§ 102 or 103 with respect to claims 1-3, 6, 8, and 10-13, because five prior art references were not considered during prosecution. Applicants also filed a proposed amendment to include the proviso that all the variables do not represent hydrogen simultaneously. The alleged purpose of the amendment was to exclude 1-amino adamantane from the subject matter covered by the claims.

On October 18, 2004, the Patent Office issued an Order Granting the Request for *Ex Parte* Reexamination. The Patent Office noted that the disclosed prior art references raised a substantial new question of patentability as to claims 1-3, 6, 8, and 10-13 because the disclosed prior art references teach and discuss the administration of adamantine derivatives (memantine or amantadine) for the treatment of cerebral disorders.

The Patent Office issued an Office Action dated March 10, 2005, finding claims 4, 5, 7, and 9 patentable. The Examiner rejected claims 1-3, 6, 8, and 10-13 as anticipated by the prior art references teaching that memantine is effective in treating cerebral ischemia and Alzheimer's disease or complications associated with the two disorders. *Office Action* at 2-3.

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In May 2005, applicants amended claim 1 to specify oral administration of an adamantane derivative to a patient diagnosed with Alzheimer's disease. *Amendment, May 9, 2005 at 2.* The applicants also added new claims 14-25. Claim 14 was directed to "a method for the treatment of cerebral ischemia comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative ...." Claim 17 was directed to "a method for the treatment of an imbalance of neuronal stimulation after Alzheimer's disease, comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative ...." Claim 20 was directed to "a method for blocking an excessive influx of calcium through NMDA receptor channels in a patient diagnosed with Alzheimer's disease ...." Claim 23 was directed to "a method for blocking the NMDA receptor in a patient diagnosed with Alzheimer's disease ...." *Id.* at 3-6.

In discussing the amended claims, the applicants noted that "[t]he present invention relates to the discovery that certain adamantane derivatives (especially memantine) can be used to treat patients diagnosed with Alzheimer's disease." *Amendment, May 9, 2005* at 8. The applicants further noted that as of May 2005, only five drugs were approved by FDA to treat patients diagnosed with Alzheimer's. Of those five drugs, none were available in 1989, and one was no longer marketed because of liver toxicity concerns. *See Id.* at 8. They also noted that memantine was the only drug approved for treatment of moderate to severe Alzheimer's disease, as well as the only such drug that did not function as a cholinesterase inhibitor. *Id.*

The Applicants also asserted that the pending claims were patentable over the prior art because the claimed methods of use provided surprising and unexpected benefits for at least three reasons: (1) in 1989, memantine was contraindicated for "severe

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confusional states," which included Alzheimer's disease patients, and was reported to cause "agitation" as a side effect, a common symptom experienced by Alzheimer's disease patients; (2) memantine was commonly believed to be a dopaminergic agent, which were thought to promote psychosis; and (3) the only published study involving the administration of memantine to Alzheimer's disease patients "plainly concluded that memantine is not effective for treatment of Alzheimer's disease." *Id.* at 10.

The Applicants argued that the Examiner improperly rejected the claims as the prior art references cited did not disclose the oral administration of memantine to a patient "diagnosed with Alzheimer's disease," as required by claim 1. Though the Applicants conceded that the Fleischhacker reference taught the administration of memantine to patients diagnosed with senile dementia of the Alzheimer type for the treatment of that condition, they argued that reference taught the administration of memantine intravenously. *See Id.* at 16-17.

Finally, the Applicants argued that the reissue claims were patentable because new claims 14-25 were narrower than the original claims, as the new claims require orally administering an adamantine derivative (claims 14-25), administering an adamantine derivative to a patient "diagnosed with Alzheimer's disease" (claims 14-25), "treatment" only (claims 14-19), treatment of an "imbalance of neuronal stimulation after Alzheimer's disease" (claims 17-19), "blocking an excessive influx of calcium through NMDA receptor channels" (claims 20-22), and "blocking the NMDA receptor" (claims 23-25). *Id.* at 17-18. The Applicants further argued that each of new claims 14-25 was patentable over the prior art because all of the claims require the step of "orally" administering an adamantine derivative to a patient "diagnosed with Alzheimer's disease." *Id.* at 18.

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The Applicants submitted two Rule 132 Declarations in support of their arguments for patentability. One declaration – from Howard Fillit, M.D. -- asserts that at the time of invention, the cholinergic approach to Alzheimer's disease treatment developed as the predominant theory, and that any proposed treatment that "strayed from this theory would have been considered extremely speculative." *Fillit Decl.* at ¶ 9. Dr. Fillit maintains that "in 1989, it would have been very surprising to find that memantine (thought to be a dopaminergic agent in 1989 and thereby unrelated to the cholinergic theory of treatment) could be successfully used for the treatment of Alzheimer's disease patients." *Id.*

Referring to the prior art relied upon by the Examiner to reject the claims, Dr. Fillit argued that "[i]f Physicians had read the [prior art references] in 1989, we would have recognized that these articles do not suggest the administration of memantine to patients diagnosed with Alzheimer's disease, which was a recognizable and diagnosable disease throughout the 1980s .... Further, by 1989, the only publication that expressly described the administration of memantine to Alzheimer's disease patients was Fleischhacker, and this article expressly concludes that memantine is not effective for the treatment of Alzheimer's disease." *Id.* at ¶ 32.

The second declaration was signed by Dr. Myron Weiner. Dr. Weiner asserted that memantine offered a number of unexpected results: (1) unexpected efficacy of a drug contraindicated for severe confusional states and having the side effect of agitation; (2) unexpected efficacy of a dopaminergic agent; and (3) unexpected existence and efficacy of NMDA antagonism. *Weiner Decl.* at ¶¶ 18-26. Dr. Weiner concluded that "[b]ased on my over 20 years experience in researching, diagnosing, and treating Alzheimer's disease patients: it was surprising and unexpected to learn that memantine could be effectively used for the treatment of patients diagnosed with Alzheimer's disease. Physicians would

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have had no reasonable expectation in 1989 that memantine could have been successfully used in this manner." *Id.* at ¶ 27.

On August 16, 2005, the Patent Office issued a Final Office Action, allowing claims 1-9 and 11-19. Claim 10 was rejected under § 112 as indefinite because it did not further limit claim 1, as amended. Claims 20-25 were rejected under § 305 as enlarging the scope of the claims of the patent being reexamined. The Examiner noted that the patent owner's amendment filed on May 9, 2005 necessitated the new grounds of rejection.

On September 26, 2005, the Examiner filed an Ex Parte Reexamination Interview Summary. The record notes simply that the outcome of the interview was embodied in an Examiner's Amendment.

On October 17, 2005, the Applicants filed an Amendment Pursuant to 37 C.F.R. §§ 1.116 and 1.530. In the Amendment, the Applicants amended claim 10 to add the limitation "wherein said adamantane derivative is memantine and said effective amount is from about 0.01 to 100 mg/kg" and cancelled claims 20-25. The Applicants also noted that in the Examiner Interview, the Examiner agreed that canceling claims 20-25 and amending claim 10 to specify the administration of memantine and its effective amount would overcome the rejection of claim 10 under § 112 and moot the rejection of claims 20-25 under § 305.

The Patent Office issued a Notice of Intent to Issue Ex Parte Reexamination Certificate on December 6, 2005. Pursuant to an Examiner's Amendment, Reissue claim 1 specifies "oral" administration of the compound to a patient "diagnosed with Alzheimer's disease," where all of the active groups (R_1, R_2, R_3, R_4, and R_5) are not all hydrogen simultaneously, and Reissue claim 10 specifies that the "adamantane derivative

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is memantine and said effective amount is from about 0.01 to 100 mg/kg." Pages 2, 3. As the reasons for allowance, the Examiner recited that the reissue claims were allowable over the prior art because those references purportedly "do not teach [that] the oral administration of ... memantine ... is effective for the prevention or treatment of cerebral ischemia in a patient diagnosed with Alzheimer's disease." Page 3.

On April 6, 2006, the Patent Office issued a Corrected Notice of Intent to Issue Ex Parte Reexamination Certificate, citing the same reasons for allowance given above.

On June 5, 2007, the Patent Office issued a Certificate of Correction to correct typographical errors.

III. NON-INFRINGEMENT ANALYSIS

A. Applicable Law

1. Claim Construction

Claims must be construed before determining whether they are valid or infringed. *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1351 (Fed. Cir. 2001); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976, 996 n. 7 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). Claims must be construed the same way for determining validity and infringement. *Id.* If possible, claims should be construed to uphold their validity. *Modine Mfg. Co. v. U.S. Int'l Trade Comm'n*, 75 F.3d 1545, 1557 (Fed. Cir. 1996).

The claim construction inquiry begins in all cases with the actual words of the claims. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (*en banc*). Claim terms are to be given their ordinary and customary meanings as they would have been understood by a person of ordinary skill in the art in the context of the patent at the time

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of the invention, i.e., as of the effective filing date of the patent application. *Id.* at 1312-14. To properly interpret claim terms, the "intrinsic" record, including the claims, the specification and the prosecution history, must be consulted (although the prosecution history may be less useful than the claims and specification). *Id.* at 1314-24. It may also be appropriate to consider "extrinsic" evidence, i.e., evidence external to the patent and prosecution history, such as expert and inventor testimony, dictionaries, and learned treatises, although extrinsic evidence is generally less reliable than the intrinsic record. *Id.* at 1317-19 and 1322-23. While there is no "magic formula," "catechism" or "rigid algorithm" for conducting claim construction, and one is not "barred from considering any particular sources or required to analyze sources in any specific sequence," one must "attach the appropriate weight" to the various sources and may not "contradict claim meaning that is unambiguous in light of the intrinsic evidence." *Id.* at 1324. The goal is to achieve correct claim construction without imposing improper limitations on the claims. *Id.* If a claim is ambiguous even after applying all of the available claim construction tools, the claim, if possible, should be construed to preserve its validity. *Id.* at 1327-28.

"Generally, the preamble does not limit the claims." *Allen Engineering Corp. v. Bartell Industries, Inc.*, 299 F.3d 1336, 1346 (Fed. Cir. 2002). A preamble that simply states the intended use of the claimed invention usually does not limit the scope of the claim. *See C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1350 (Fed. Cir. 1998). "If the preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as limiting." *Allen Engineering Corp.*, 299 F.3d at 1346 (citing *Kropa v. Robie*, 187 F.2d 150, 152 (CCPA 1951)).

A dependent claim must incorporate all of the limitations of and be narrower in scope than the claim from which it depends. *See Jeneric/Pentron, Inc. v. Dillon Co., Inc.*,

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205 F.3d 1377, 1383 (Fed. Cir. 2000) (A "dependent claim, by nature, incorporates all the limitations of the claim to which it refers."); *Desper Prods., Inc. v. Qsound Labs, Inc.*, 157 F.3d 1325, 1338 n.5 (Fed. Cir. 1998) (dependent claims "necessarily must be narrower than the independent claims").

2. Infringement Law

Once a claim has been construed, it is compared to an accused product or method to determine whether that product or method infringes the claim. *Markman*, 52 F.3d at 976. To establish infringement, every claim limitation or its equivalent must be found in an accused product or method. *Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*, 520 U.S. 17, 29, 40 (1997). Infringement must be proved by a preponderance of the evidence. *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241. If a claim "reads on" an accused product or method, *i.e.*, the accused product or method embodies each limitation set forth in the claim exactly, the accused product or method is said to literally infringe the claim. *Cole v. Kimberly-Clark Corp.*, 102 F.3d 524, 532 (Fed. Cir. 1996).

Infringement may also be found under the doctrine of equivalents if the accused product or method includes features that are identical or equivalent to each claimed element. *Warner-Jenkinson*, 520 U.S. at 21 and 40. The determination of equivalency, which is evaluated as of the time of infringement, is an objective inquiry applied on an element-by-element basis taking into account the role of each claim element in the context of the claim. *Id.* at 18, 29, 37 and 40.

The Supreme Court has not mandated any specific approach for evaluating equivalency. *Id.* at 39-40. Among the recognized approaches that may be applied are the so-called triple identity (function-way-result) test, the insubstantial differences test and/or

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the important objective factor of known interchangeability. *Id.* at 19-20, 25, 36 and 39-40.

There are a number of limits on the application of the doctrine of equivalents. For example, the doctrine of equivalents cannot be applied so as to effectively eliminate a claim limitation in its entirety. *Warner-Jenkinson*, 520 U.S. at 29. Moreover, limitations may not be afforded a scope of equivalency that effectively results in a claim that does not patentably distinguish the prior art. See, e.g., *Wilson Sporting Goods Co. v. David Geoffrey & Associates*, 904 F.2d 677, 683 (Fed. Cir. 1990). Additionally, prosecution history estoppel operates to prevent recapture, through the doctrine of equivalents, of coverage of subject matter that was relinquished by amendment or argument during prosecution. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 733-34 (2002).

Pursuant to 35 U.S.C. § 271(b), "whoever actively induces infringement of a patent shall be liable as an infringer." Interpreting this section, the Court of Appeals for the Federal Circuit requires the plaintiff to prove that the defendant's "'actions induced infringing acts and that [they] knew or should have known [their] actions would induce actual infringement.'" *Warner-Lambert Company v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003) (citing *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990)). However, the Federal Circuit has also concluded that "'knowledge of the acts alleged to constitute infringement is not enough.'" *Id.* Rather, a finding of active inducement requires proof of actual intent to cause the acts which constitute the infringement. *Id.* Thus, "'inducement requires proof that the accused infringer knowingly aided and abetted another's direct infringement of the patent.'" *Id.* (citing *Rodime PLC v. Seagate Tech., Inc.*, 174 F.3d 1294, 1306 (Fed. Cir. 1999)). Inducement

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of infringement also requires the commission of an act that constitutes inducement, and not merely the power to act or the failure to act. *See Beverly Hills Fan Co. v. Royal Sovereign Corp.*, 21 F.3d 1558, 1569 (Fed. Cir. 1994).

B. Analysis of the '703 Patent Claims

1. Construction of the '703 patent claims

According to their plain meaning, claims 1-13 are directed to, *inter alia*, a method for the prevention or treatment of cerebral ischemia comprising the step of orally administering an adamantane derivative to a patient diagnosed with Alzheimer's disease. Claims 14-16 are directed to, *inter alia*, a method for the treatment of cerebral ischemia comprising the step of orally administering an adamantane derivative to a patient diagnosed with Alzheimer's disease.

The Online Medical Dictionary[2] defines "cerebral ischemia" as "deficiency in blood supply to the brain." The specification indicates that the claims are not directed to a method of treating a deficiency in blood supply to the brain, however, but rather a method of treating or preventing degeneration and nerve loss resulting from cerebral ischemia:

> [C]erebral ischemia is characterized by a pathophysiological situation defined by an imbalance of neuronal stimulation mechanisms. In this context, the excessive inflow of calcium through NMDA receptor channels finally leads to the destruction of brain cells in specific brain areas.

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[2] Available online at: http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=&action=Home.

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> Therefore, in order to treat or eliminate this pathological situation, an antagonistic intervention is required with regard to the NMDA receptor channels.

'703 *patent* at col. 2, l. 46-55 (citations omitted). The specification then explains that:

> The present invention is aimed at preparing and employing compounds which can be chemically generated by simple methods, exhibiting an NMDA receptor channel-antagonistic and anticonvulsive action, for use in the prevention and treatment of cerebral ischemia.
>
> * * * *
>
> It has been found unexpectedly that the use of these compounds prevents an impairment or further impairment, i.e., degeneration and loss of nerve cells. Therefore, the adamantane derivatives of formula (I) are especially suited for the prevention and treatment of cerebral ischemia after . . . Alzheimer's disease.

Id. at col. 2, l. 67 – col. 3, l. 16.

The '703 patent purports to show the efficacy of the claimed methods of use for the adamantane derivatives in a pharmacological test titled "Protection Against Cerebral Ischemia." '703 *patent* at col 6, ln 27-64. In that test, both carotid arteries of a rat are occluded and the blood pressure is lowered by withdrawal of blood for ten minutes. "The ischemia is terminated by opening the carotids and reinfusion of the withdrawn blood." *Id.* It was well-known that periods of cerebral ischemia lead to large increases in

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extracellular concentrations of glutamate and aspartate resulting in neuronal brain damage. *Kemp et al., TIPS, 1987, 8, 414-15.* It was also well-known that this imbalance of excitatory amino acids leads to an excessive stimulation of the NMDA receptors, leading to a lethal accumulation of intracellular calcium ions and brain cell death. *Id.* The '703 patent similarly recites that cerebral ischemia results in an imbalance of neuronal stimulation mechanisms that results in excessive inflow of calcium through the NMDA receptor channel leading to the destruction of brain cells. *'703 patent* at col. 2, l. 46-52. In discussing the carotid artery results, the '703 patent specification concludes that "the test results show that the compounds according to formula (I) exhibit a neuroprotective action in cerebral ischemia." *Id.* at col. 6, l. 58-60.

Claims 17-19 are directed to a method for the treatment of an "imbalance of neuronal stimulation after Alzheimer's disease, comprising orally administering to a patient diagnosed with Alzheimer's disease" an adamantane derivative. In the May 2005 Amendment, the applicants indicated that, "[a]s defined in the '703 patent, 'cerebral ischemia' refers to an imbalance of neuronal stimulation in which an excessive influx of calcium through NMDA receptor channels leads to degeneration and loss of brain cells." *Id.* at 18. Accordingly, the methods of claims 17-19 are directed to the treatment of cerebral ischemia in a patient diagnosed with Alzheimer's disease.[3]

The '703 patent is predicated on the notion that Alzheimer's disease (among other conditions) is a cause of cerebral ischemia. Thus, the specification indicates that the use of adamantane derivatives "prevents an impairment or further impairment, i.e., degeneration and loss of nerve cells, after ischemia," and that adamantane derivatives are

[3] Claims 17-19 differ from claim 1 (and the claims dependent thereon) because claim 1 encompass methods of "prevention or treatment of cerebral ischemia," whereas claims 17-19 are limited to methods of treatment.

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"especially suited for the prevention and treatment of cerebral ischemia after ... Alzheimer's disease." *'703 patent* at col 3, ln 7-16. In light of the plain language of the claims and the specification, the claims of the '703 patent are directed to a method for the treatment or prevention of neurodegeneration resulting from cerebral ischemia caused by Alzheimer's disease.

The prosecution history confirms that the claims of the '703 patent are directed to a method for the treatment and prevention of neurodegeneration resulting from cerebral ischemia after Alzheimer's disease. For instance, in the May 2005 Amendment, the applicants amended claim 1 to include the limitation "diagnosed with Alzheimer's disease" and referred to column 3, lines 7-16 and claim 10 as written support for that proposed claim element. The Applicants maintained that claims 14-16 were distinguished from cited prior art because the prior art did not disclose or suggest the treatment of "cerebral ischemia" and that claims 17-19 were distinguished because the prior art did not teach or suggest the treatment of an "imbalance of neuronal stimulation after Alzheimer's disease." In the August 2005 Office Action, the Examiner accepted the Applicant's arguments, indicating that "the prior art does not actually teach any of the adamantane derivatives to treat cerebral ischemia and Alzheimer's disease ***together***." *August 16, 2005 Office Action* at 2, (emphasis added). And the Examiner rejected claim 10, which at the time was directed to a "method of claim 1 for the treatment of Alzheimer's disease," for not further limiting claim 1 as amended to include the recitation "diagnosed with Alzheimer's disease." For these reasons, each of the '703 patent claims is limited to a method for preventing or treating neuronal degeneration resulting from cerebral ischemia in a patient with Alzheimer's disease.

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2. Orchid's Proposed Generic Memantine Products Will Not Infringe Any Valid Claim of the '703 Patent

(a) **Claims Encompassing Memantine**

Orchid's proposed labeling indicates that it does not seek approval for its proposed generic memantine product for the treatment of cerebral ischemia, nor will it be indicated for use in the treatment of cerebral ischemia. Nor will Orchid's proposed memantine product be indicated for the treatment of cerebral ischemia in patients with Alzheimer's disease, as required by the claims of the '703 patent. Orchid's proposed product will be indicated for treatment of dementia of the Alzheimer's type. The proposed indication for Orchid's generic memantine product accordingly is distinct from the claimed methods of the '703 patent (insofar as those claims encompass methods of using memantine) because the claimed methods necessarily involve "employing compounds . . exhibiting an NMDA receptor channel-antagonistic and anticonvulsive action, for use in the treatment and prevention of cerebral ischemia." *'703 patent* at col. 2, l. 67 – col. 3, l. 3.

Moreover, the claimed methods of the '703 patent require the use of memantine to prevent "degeneration and loss of nerve cells, after ischemia." *Id.* at col. 3, l. 9-10. Orchid's proposed product label will indicate that there is no evidence that its proposed generic memantine product "prevents or slows neurodegeneration in patients with Alzheimer's disease." In fact, there are no known methods for treating the underlying cause of Alzheimer's disease.[4] For these reasons, Orchid's proposed memantine product will not infringe any valid claim of the '703 patent.

[4] http://www.nia.nih.gov/Alzheimers/AlzheimersInformation/Treatment/.

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Orchid's proposed memantine product will not infringe any valid claim of the '703 patent under the doctrine of equivalents because attempting to do so would effectively eliminate the claim limitation "treatment of cerebral ischemia" in its entirety. Moreover, the doctrine of equivalents may not be used to encompass Orchid's proposed memantine product because doing so would create a scope of equivalency that effectively results in a claim that does not patentably distinguish the prior art. Additionally, prosecution history estoppel operates to prevent the use of the doctrine of equivalents to cover Orchid's proposed memantine product because of amendments and arguments made during prosecution. For example, the patentee is estopped from arguing that the claims of the '703 patent cover the administration of memantine for the treatment of moderate to severe dementia of the Alzheimer's type because during prosecution the applicants asserted their claims were distinguished from the prior art Fleischhacker article, which they admitted discloses the administration of memantine to treat senile dementia of the Alzheimer's type, on the grounds that the claims of the '703 patent were limited to the administration of adamantane derivatives for the treatment of cerebral ischemia and the administration of memantine for the treatment of Alzheimer's disease. *See 8/18/2004 Request for Reexamination* at 8. Forest further argued that the claims were limited to the treatment of cerebral ischemia in order to overcome a § 102 rejection. *See 5/9/2005 Amendment* at 10 & 18. The Examiner ultimately agreed, allowing the claims on the basis that "the prior art does not actually teach any of the adamantane derivatives to treat cerebral ischemia and Alzheimer's disease together." *See 8/16/2005 Office Action*. For these reasons, Orchid's proposed generic memantine product will not infringe claims 1-3, 6, 8, and 10-19 of the '703 patent.

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(b) **Claims to the Use of Compounds Other Than Memantine**

Claims 4, 5, 7, and 9 of the '703 patent are limited to methods of administering compounds other than memantine. For the general formula shown in claim 1, claim 4 requires that R_3 and R_4 be an ethyl substituent, claim 5 requires that R_3 be an ethyl, isopropyl, or cyclohexyl substituent, claim 7 requires that R_1 be a methyl or ethyl substituent, and claim 9 requires that R_3 be an ethyl substituent. As noted by Forest, memantine is represented by the general formula shown in claim 1 when R_1 and R_2 are hydrogen, one of R_3, R_4, and R_5 is hydrogen and the remaining two of R_3, R_4, and R_5 are methyl. *See Request for Extension of Patent Term, December 9, 2003* at 6. Thus, Orchid's proposed generic memantine product will not infringe claims 4, 5, 7, and 9 of the '703 patent.

IV. INVALIDITY ANALYSIS

A. Validity Law

A U.S. patent is presumed to be valid pursuant to 35 U.S.C. § 282. The presumption of validity can be overcome, but only by clear and convincing evidence that the patent is invalid. *Sibia Neurosciences, Inc. v. Cadus Pharmaceutical Corp.*, 225 F.3d 1349, 1355 (Fed. Cir. 2000). The bases for holding a patent invalid include, among others, that the claims are anticipated by or would have been obvious in view of the prior art as discussed below, that the patent specification does not fully and sufficiently describe the invention (in violation of 35 U.S.C. § 112, first paragraph), and that the claims are indefinite (in violation of 35 U.S.C. § 112, second paragraph). In the case of

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prior art-based invalidity, the clear and convincing burden of proof may be more easily met through reliance upon prior art that was not before the examiner during prosecution. *Sibia Neurosciences, id.* at 1355-56. However, patent claims nonetheless have been held invalid based upon prior art that was before the examiner. *E.g., Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1319, 1322 n.2, 1325 (Fed. Cir. 2004) (claims obvious in view of the same and cumulative prior art); *Brown v. 3M*, 265 F.3d 1349, 1351-54 (Fed. Cir. 2001) (claim anticipated by the same prior art); *Celeritas Tech. Ltd v. Rockwell Int'l Corp*, 150 F.3d 1354, 1360-61 (Fed. Cir. 1998) (claims anticipated by the same prior art).

Prior art may be in a number of forms. For example, the prior art may be (1) a patent or printed publication in the United States or a foreign country, or a public use or offer for sale in the United States, more than one year before the earliest effective U.S. filing date of the patent (35 U.S.C. §102(b)); or (2) a patent granted on, or a publication of, a patent application by another filed in the United States before the invention thereof by the applicant (35 U.S.C. §102(e)). Other examples are provided in 35 U.S.C. §102.

If all claimed elements/steps are disclosed, expressly or inherently, in a single prior art reference, that reference is said to "anticipate" the claimed invention, thereby invalidating the claim(s) under 35 U.S.C. §102 for lack of novelty. *Transclean Corp. v. Bridgewood Services, Inc.*, 290 F.3d 1364, 1370 (Fed. Cir. 2002). The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). If granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated, regardless

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of whether it also covers subject matter not in the prior art. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 781 (Fed. Cir. 1985).

In the absence of an anticipatory prior art reference, the issue becomes whether "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). In determining obviousness, the following four factors must be considered: (1) the scope and content of the prior art; (2) any differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) any secondary considerations evidencing non-obviousness, such as commercial success, copying, long felt but unsolved needs, failures of others, unexpected results, etc. *KSR Intl Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1391 (2007), *citing Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

In *KSR*, the Supreme Court confirmed that, in evaluating obviousness, "an expansive and flexible" approach is to be taken, *i.e.*, "rigid and mandatory formulas" are improper. 82 USPQ2d at 1395-97. More specifically, the Court indicated that combining prior art elements to perform their respective established functions is likely to be obvious when it does no more than yield predictable results. *Id.* at 1395. Indeed, if a design need or market pressure to solve a problem having a finite number of identified, predictable solutions provides good reason for an ordinarily skilled person to pursue the known options within his or her technical grasp, and if such pursuit leads to the anticipated success, "it is likely the product not of innovation but of ordinary skill and common sense" and "[i]n that instance the fact that a combination was obvious to try might show that it was obvious under §103." *Id.* at 1397. Conversely, when the prior art teaches

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away from combining known elements, discovery of a successful way to combine them is more likely not obvious. *Id.* at 1395.

Obviousness is not shown merely by demonstrating that each of the elements of a claimed combination was known in the art. Rather, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine [or modify] the elements" as claimed. *Id.* at 1396. However, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent" can provide such a reason, as the applicant's particular motivation/purpose does not control. *Id.* at 1397. Also, a precise teaching of claimed subject matter is not needed, as familiar items have obvious uses beyond their primary purposes, and one must consider inferences/creative steps that a person of ordinary skill ("a person of ordinary creativity, not an automaton") would have employed. *Id.* at 1396-97.

The level of skill in the art is determined entirely with reference to a hypothetical person of ordinary skill in the art presumed to be aware of all of the pertinent prior art. Relevant factors in determining the level of skill include the educational level of active workers in the field, the type of problems encountered in the art, prior art solutions to such problems, the rapidity of innovations in the art, and the sophistication of the technology. *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). Determination of the level of skill is often critical to determinations of whether prior art is "analogous art" and whether one of ordinary skill in the art would have been motivated to combine (or modify) prior art references. *DyStar*, 464 F.3d at 1361-63, 1370.

In order for secondary considerations evidence to be given substantial weight, the applicants must demonstrate that there is a nexus between such evidence and the merits

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of the claimed invention. *Ormco*, 463 F.3d at 1311-13; *GPAC*, 57 F.3d at 1580. In other words, such evidence must arise from the claimed invention, rather than from extrinsic influences such as unclaimed features, prior art features, marketing activities, etc. *Id.* (and cited cases).

B. Analysis of the '703 Patent Claims

1. The Claims of the '703 Patent Are Obvious in Light of the Prior Art

The claims of the '703 patent are invalid as obvious in light of the prior art. As discussed above, all claims of the '703 patent are limited to a method for preventing or treating neuronal degeneration resulting from cerebral ischemia in a patient with Alzheimer's disease. The prior art teaches both the treatment of cerebral ischemia and the treatment Alzheimer's disease patients with memantine. Taking at face value the assertions in the '703 patent that Alzheimer's disease causes cerebral ischemia and that memantine prevents neuronal degeneration resulting from the Alzheimer's-induced ischemia, then treating an Alzheimer's patient with memantine would inherently treat any neuronal degeneration resulting from the Alzheimer's-induced ischemia.

The use of memantine to treat cerebral ischemia was well-known prior to the priority date of the '703 patent. For instance, Wesemann et al, *Arzneimittelforschung*/Drug Res. 1983, 33(8), 1122 teaches that memantine is clinically useful in the treatment of cerebrovascular disorders. In addition, Weseman et al. *J Neural Transm Suppl.* 1980;(16):143 teaches that a patient with arteriosclerotic Parkinson syndrome was treated successfully with memantine. Miltner, *Arzneimittelforschung*/Drug Res. 1982, 32(10), 1268, reports that comatose patients suffering from post-traumatic cerebrovascular complications were successfully treated

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with memantine. The *Rote Liste 1986* indicates that memantine is useful to treat cerebrovascular disorders. Marcea *et al.*, *Therapiewoche*, 1988, 38, 3097-3100[5] cites to earlier studies that show that elderly patients with degenerative or vascular cerebro-organic disorders continuously show impressive improvements when given memantine.

Although the use of memantine to treat neurodegeneration resulting from Alzheimer's disease was (and still is) unknown, the administration of memantine to patients having Alzheimer's disease also was well-known prior to the priority date of the '703 patent. For example, Fleischhacker *et al.*, *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 196, 10, 87-93, describes a clinical study that administered memantine to patents who were diagnosed with senile dementia of the Alzheimer's type.

A number of other references contain similar teachings. Thus, the Marcea article describes a clinical study in which memantine was orally administered successfully to elderly patients diagnosed with moderately severe organic brain syndrome, or dementia, diagnosed according to the ICD.9 criteria. *Marcea translation* at 2. The ICD.9 criteria include dementia of the Alzheimer's type. *Fillit Declaration, May 5, 2005* at 6. Indeed, Alzheimer's disease is the most common cause of dementia; it accounts for > 65% of dementias in the elderly.[6] Thus, one of ordinary skill would have understood that most patients diagnosed with dementia are patients with Alzheimer's disease. Ambrozi *et al.*, *Pharmacopsychiatry*, 21:144-46 (1988), describes a clinical study involving geriatric inpatients diagnosed with dementia where one-half of the patients were successfully administered memantine and the other half were administered a placebo. Tempel,

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[5] Based on Forest translation submitted during reexamination of the '703 patent.

[6] The Merck Manual: http://www.merck.com/mmpe/sec16/ch213/ch213c.html?qt=dementia&alt=sh.

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Memantine Workshop March 20-21, 1987, 23-26, describes a clinical study comparing successful treatment of memantine at 10 mg per day to a more successful treatment at 20 mg per day in 60 elderly patients with an organic psychosyndrome indication. Organic brain syndrome includes dementia of the Alzheimer's type.[7] The *Rote Liste 1986* also indicates that memantine is useful to treat organic brain syndrome. Meldrum et al., *Naunyn Schmiedebergs Arch Pharmacol.* 1986, 332(1), 93-7, teaches that memantine is effective in the treatment of parkinsonism and that it enhances vigilance, short-term memory and mood in geronto-psychiatric patients. Wesemann et al, *Arzneimittelforschung*/Drug Res. 1982, 32(10), 1241-43 teaches that memantine improves disturbances of the extrapyramidal system and that it enhances parameters like vigilance, short-term memory, and mood in geronto-psychiatric patients. Thus, considering that Alzheimer's disease accounts for > 65% of the cases of dementia among the elderly such that most of the patients in these studies likely had Alzheimer's disease, one of ordinary skill would have understood that the above studies describe the successful administration of memantine to patients with Alzheimer's disease.

The foregoing references illustrate methods of using memantine to successfully treat cerebral ischemia and to successfully treat patients diagnosed with Alzheimer's disease, before the priority date of the '703 patent. Accordingly, it would have been obvious as of the effective filing date of the '703 patent application for one of ordinary skill in the art to utilize memantine to treat both conditions – *i.e.*, to orally administer memantine to prevent or treat cerebral ischemia in a patient diagnosed with Alzheimer's disease at the dosage levels set forth in the claims of the '703 patent.

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[7] http://www.nlm.nih.gov/medlineplus/ency/article/001401.htm

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2. The Claims of the '703 Patent Alternatively Are Invalid As Anticipated or Obvious

As noted, Orchid's proposed generic memantine product will not infringe any claim of the '703 patent because those claims are properly construed to claim a method for preventing or treating neuronal degeneration resulting from cerebral ischemia in a patient with Alzheimer's disease. Forest Labs appears to construe certain of the claims more broadly, however, suggesting that at least claim 10 of the '703 patent "remains explicitly directed to the treatment of Alzheimer's disease." *Supplement to Request for Extension*. Dec. 27, 2006 at 2. While that characterization ignores the plain language of the '703 patent claims (including claim 10), in the event that one or more claims of the '703 patent are construed to merely be "directed to the treatment of Alzheimer's disease," then the claims alternatively would be invalid over prior art from Fleischhacker, Marcea, Ambrozi and Tempel.

Assuming one or more of the claims of the '703 patent are construed to merely be "directed to the treatment of Alzheimer's disease," as Forest Labs has asserted, any such claims would be obvious in light of Fleischhacker, who describes a five-week clinical study that included 20 patents with an average age of 77.5 years who were diagnosed with senile dementia of the Alzheimer's type. Fleischhacker *et al., Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 196, 10 at 88. Ten of the patients were treated with memantine at a daily dosage of 20 to 30 mg for a period of 35 days to determine its efficacy in the treatment of dementia of the Alzheimer's type. *Id.* at 87 – 88. The criteria used to assess outcome were the Clinical Global Impression, which assessed attention and short term memory, and the Geriatric Rating Scale and the Sandoz Clinical Assessment Geriatric, which quantified psychopathology and behavior. *Id.* at 88. In the memantine group, five patients improved, three remained the same, and only

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two deteriorated, while in the placebo group, only four patients improved, three remained the same, and three deteriorated. *Id.* at 89. While the memantine and placebo groups reportedly are not statistically distinguishable, the study's authors conclude that long-term studies could probably show clear distinction between the two groups. *Id.* at 89. The authors suggest that further studies should also be done with patients having less severe forms of dementia. *Id.* The Fleischhacker article therefore teaches a method of using memantine in the treatment of dementia of the Alzheimer's type.

Although the Fleischhacker trial involved the intravenous administration of memantine, it would have been an entirely obvious design choice as of April 1989 to administer the compound orally. For example, the Marcea reference teaches the oral administration of memantine. *Marcea translation* at 2. In fact, *Rote Liste 1986* indicates that memantine was commercially available in the form of tablets for oral administration. In addition, neither the Ambrozi nor Tempel articles indicate that patients were treated with memantine other than by oral administration. Indeed, oral administration of a drug was most commonly used because of its convenience. *See Basic and Clinical Pharmacology*, 4th ed., Katzung Ed., 1989, Appleton & Lange at p. 4. In addition, one of ordinary skill in the art would have been motivated to use orally-administrated memantine to treat patients with dementia of the Alzheimer's type because oral administration was known to result in memantine concentrations remaining in the brain for much longer periods of time compared to i.v. administration.[8] Thus, one of ordinary skill in the art would have been motivated to orally administer memantine to treat

[8] For example, Wesemann et al., *Arzneimittelforschung*. 1982;32(10):1243 describes memantine concentrations in the rat brain after both i.v. and p.o. administration. Wesemann shows that in contrast to the rapid concentration decrease in the brain after i.v. administration, a plateau is reached 1 hour after p.o. administration of memantine and maintained at least for the first 4 hours. Weseman also notes that its findings are in accordance with those seen in a human patient.

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dementia of the Alzheimer's type with an expectation of success in light of Fleischhacker.

The clinical studies and results reported on the Namenda® package insert are similar to the clinical studies described in the prior art Fleischhacker, Marcea, Ambrozi and Tempel articles—the main differences being the length of time and number of patients. The two U.S. clinical studies discussed in the package insert rely in part on measurements of Severe Impairment Battery, which measures "selected aspects of cognitive performance, including elements of attention, orientation, language, memory, visuospatial ability, construction, praxis, and social interaction." *Namenda Package Insert at 1*. The earliest of the studies reported on the Namenda® package insert is a 12-week study done in Latvia. The Latvia study enrolled 166 patients between 60 and 80 years of age that were demented as defined by DSM-III. Forty-nine percent of the patents had a Hachinski Ischemic Scale (HIS) score of less than 5 and were deemed to possibly have Alzheimer's disease, while the remaining patients with a HIS score greater or equal to 5 were deemed to have mixed type or vascular dementia. Two criteria were used to assess outcome in the Latvia study: the Clinical Global Impression of Change (CGI-C), which is the clinician's impression of severity of illness and the Behavioral Rating Scale for Geriatric Patients (BGP), which is an observer-rated scale for the assessment of functional and behavioral disturbances of geriatric patients. *See* Winblad and Poritis, *Int. J. Geriat. Psychiatry*, 1999, 14, 135. The prior art clinical studies, like the Latvia study, include geriatric patients with dementia, where a subset of the patents possibly have Alzheimer's disease. The patients in the prior art studies were evaluated using the same or similar criteria as those used in the Latvia study. And like the Latvia study, the patents treated with memantine in the prior art studies showed improvement when evaluated by similar criteria.

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Marcea *et al.*, *Therapiewoche*, 1988, 38, 3097-3100 describes a six-week clinical study involving 60 patients over the age of 55 diagnosed with moderately severe organic brain syndrome according to ICD.9 criteria, which includes dementia of the Alzheimer's type. One-half of the patients were orally administered tablets of memantine and the other half were administered a different drug. The main criteria of the study were the performance and judgment of the patients and their orientation, which were based on the following psychometric scales: the Functional Psychosis Scale B, the Plutchik Geriatric Rating Scale, and the Sandoz Clinical Assessment Geriatric Scale. The study showed a clinically relevant improvement for the patients in both groups, with the patients receiving memantine showing the most improvement. *Marcea translation* at 3-5.

Ambrozi *et al.*, *Pharmacopsychiatry*, 1988, 21, 144 describes a clinical study involving 30 inpatients diagnosed with dementia according to DSM-III where one-half of the patients were administered memantine and the other half were administered a placebo. The purpose of the study was to determine whether memantine has the ability to influence the amnestic disorders characteristic of dementia as one category of the organic mental disorders (DSM-III). The main criteria of the study were vigilance, short-term memory, and concentration, which were determined by a flicker frequency analysis, a digit span test, and mosaic test. A psychiatric rating scale was also used as a criterion. The Ambrozi article reports significant improvements in vigilance, short-term memory, and concentration for the patients administered memantine.

Tempel, *Memantine Workshop March 20-21*, 1987, 23-26 describes a nine-week clinical study comparing treatment of memantine at 10 mg per day to treatment at 20 mg per day in 60 patients between the ages of 60 and 80 with an organic psychosyndrome

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indication. Organic brain syndrome includes dementia of the Alzheimer's type.[9] The study used physical symptoms and psychometric scales as the two criteria to assess outcome. The study reports an equivalent improvement in both treatment groups for physical symptoms and for the Profile of Mood States, a self-evaluation scale. The study reports improvement for both groups when assessed according to the Sandoz Clinical Assessment Geriatric Scale, with the 20 mg group appearing to show more improvement that the 10 mg group.

Considering that Alzheimer's disease accounts for > 65% of cases of dementia in the elderly,[10] one of ordinary skill in the art would have understood that most of the dementia patients treated in these studies had Alzheimer's disease (or dementia of the Alzheimer's type). Indeed, in the Latvia clinical study used to support Namenda's indication for treatment of dementia of the Alzheimer's type, 49% of the patients with dementia according to DSM-III in the Latvia study were deemed to have possible Alzheimer's disease. Thus, in the event that one or more claims of the '703 patent are construed to merely be "directed to the treatment of Alzheimer's disease," such claims would be invalid as obvious over at least the prior art Fleischhacker, Marcea, Ambrozi and Tempel references.

3. The Claims of the '703 Patent Are Invalid for Lack of Enablement and/or Utility

35 U.S.C. § 112 requires that:

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[9] http://www.nlm.nih.gov/medlineplus/ency/article/001401.htm

[10] The Merck Manual: http://www.merck.com/mmpe/sec16/ch213/ch213c.html?qt=dementia&alt=sh.

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> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The Federal Circuit has held that "the enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1378 (Fed. Cir. 2007) (citations omitted). As the Federal Circuit explained "the how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention." *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999), quoting *In re Ziegler*, 992 F.2d 1197, 1200 (Fed. Cir. 1993); *see also In re Schoenwald*, 964 F.2d 1122, 1124 (Fed. Cir. 1992) (stating that utility must be disclosed to satisfy the section 112 enablement requirement). In explaining what constitutes a sufficient showing of utility in the context of the enablement requirement, the Federal Circuit has stated that an applicant's failure to disclose how to use an invention may support a rejection under either section 112, paragraph 1 for lack of enablement, or "section 101 for lack of utility 'when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention.'" *Cortright*, 165 F.3d at 1356, quoting *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762 (Fed. Cir. 1984).

The claims of the '703 patent require the prevention or treatment of neuronal degeneration resulting from cerebral ischemia in a patient with Alzheimer's disease or,

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alternatively, they are merely "directed to the treatment of Alzheimer's disease." In either event, "there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention.'" *Cortright*, 165 F.3d at 1356. Thus, the specification of the '703 patent fails to provide any data indicating that the administration of memantine (or any adamantane derivative) effectively treats neuronal degeneration in a patient with Alzheimer's disease. Moreover, there is no data in the '703 patent that any symptoms resulting from Alzheimer's disease can be prevented or treated. The only mention of Alzheimer's disease in the specification is at the end of a list of conditions that purportedly cause cerebral ischemia. *See '703 patent at col. 3, l. 10-16*. The examples in the '703 patent are allegedly directed to showing efficacy in the prevention of the destruction of brain cells following an event of cerebral ischemia. *See id. at col. 6, l. 28-63*. There are, however, no examples directed to or evidencing neuroprotection in a patient diagnosed with Alzheimer's disease or any animal model reasonably approximating that disease state. *See id. at passim*. Indeed, the '703 patent specification is devoid of any data directed to or evidencing the notion that the referenced compounds effectively treat dementia of any type. *See id. at passim*.

The '703 patent specification does not contain data supporting the claimed use of memantine to prevent or treat neuronal degeneration resulting from cerebral ischemia in a patient with Alzheimer's disease or, alternatively, "the treatment of Alzheimer's disease" alone. There is no data of the sort set forth in the prior art references described above. In fact, there is no data of any type evidencing that memantine could be used to treat dementia. Moreover, Alzheimer's disease is a complex disease and "[w]hat causes degeneration of brain tissue in Alzheimer's disease is unknown." *Merck Manual of Health & Aging*, Section 3, chapter 27. In fact, there is no known treatment for the

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neurodegeneration associated with Alzheimer's disease.[11] The absence of information describing to one of skill in the art that the claimed invention actually prevents or treats Alzheimer's disease (or dementia of the Alzheimer's type) therefore renders the claims of the '703 patent invalid under 35 U.S.C. § 112 and/or § 101. There is no indication that one skilled in the art would accept without question the unsupported statement that the compounds identified in the '703 patent could be used to treat Alzheimer's disease (or dementia of the Alzheimer's type). Therefore, the applicants have failed to demonstrate sufficient utility and therefore cannot establish enablement. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005). For these reasons, the claims of the '703 patent are invalid.

V. CONCLUSION

For the reasons discussed above, Orchid's proposed product would not infringe any valid claim of the '703 patent, either literally or under the doctrine of equivalents. Furthermore, the claims of the '703 patent are invalid in light of the prior art and for lack of enablement and/or lack of utility.

Very Truly Yours,

Dr. Billa Praveen Reddy,
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[11] http://www.nia.nih.gov/Alzheimers/AlzheimersInformation/Treatment/

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Exhibit 33

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BY EMAIL AND FEDERAL EXPRESS

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Re: **Orchid Chemicals & Pharmaceuticals Ltd.'s ANDA No. 90-044**
Notice of Paragraph IV Certification
U.S. Patent No. 5,061,703

Dear Dr. Reddy:

Together with Jones Day, we represent both Forest Laboratories, Inc. ("Forest") and Merz Pharma GmbH & Co. KGaA ("Merz"). On or about December 11, 2007, we received Orchid Chemicals & Pharmaceuticals Ltd.'s ("Orchid") Paragraph IV Certification Notice for U.S. Patent 5,061,703 . In response, we request an unredacted copy of the ANDA referred to therein (ANDA No. 90-044) and associated Drug Master File(s). In addition, please promptly forward the items listed below to my attention for evaluation and testing:

1. One hundred (100) samples of each strength of Orchid's Memantine Hydrochloride tablets, 5 mg and 10 mg ("Orchid's proposed tablets");

2. Ten grams (10 g) from each of six (6) lots of the Active Pharmaceutical Ingredient ("API") to be used in Orchid's proposed tablets; and

3. Ten grams (10 g) from each of six (6) lots of each excipient to be used in Orchid's proposed tablets.

These materials are necessary so that we may evaluate the claims in Orchid's Paragraph IV Certification Notice.

Thank you for your assistance in this matter. Please feel free to contact me if you have any questions.

Sincerely,

Andres Sawicki

cc: Jake Holdreith, Esq.
Gerald J. Flattmann, Esq.
Charles S. Ryan, Ph.D., J.D.
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SIGN: Andres Sawicki
EIN/VAT:

SHIP TO: 2124466427 BILL SENDER

Dr. Billa Praveen Reddy
Orchid Chemicals & Pharmaceuticals
Sipcot Industrial Park
Irungattukotai

Kancheepuram Distric, 602105
IN

TRK# 0430 7992 4995 5984

PM
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From: Origin ID: JRBA (212) 446-6427
Andres Sawicki
Kirkland & Ellis LLP
153 East 53rd Street
38th Floor
New York, NY 10022
UNITED STATES

FedEx Express

CLS30507/21/23

Ship Date: 04JAN08
ActWgt: 1 LB
System#: 5564804/INET7091
Account#: S *********
TotWgt: 1 LB

REF: 40844-0025
DESC-1: Correspondence/No Customs Value
DESC-2:
DESC-3:
DESC-4:
EEI: NO EEI 30.37(a)
COUNTRY MFG: US
CARRIAGE VALUE: .00 USD
CUSTOMS VALUE: USD
T/C: S 133267956 D/T: S 133267956
SIGN: Andres Sawicki
EIN/VAT:

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Exhibit 34

From: KENNETH.SCHULER@lw.com [mailto:KENNETH.SCHULER@lw.com]
Sent: Thursday, January 31, 2008 6:03 PM
To: Blumenfeld, Jack; DMoore@potteranderson.com
Cc: RHorwitz@potteranderson.com; ntarantino@Potteranderson.com; mbaker@potteranderson.com
Subject: RE:

No Plaintiff has ever taken the position in a case I have been involved with that Orchid was required to appoint such an agent. In fact, your co-counsel in the present case appears to have taken the opposite position in a case pending in NJ involving desloratadine. Therefore, I am not aware of any need for them to appoint such an agent, nor whom they would designate if they were to conclude that one was appropriate. I could ask them, but in addition to being contrary to how others have treated the issue, what would be the point given our willingness to accept service of this particular complaint? In any event, it is the middle of the night in India, and I would not get an answer today.

From: Blumenfeld, Jack [mailto:JBlumenfeld@MNAT.com]
Sent: Thursday, January 31, 2008 4:48 PM
To: Schuler, Kenneth (CH); DMoore@potteranderson.com
Cc: RHorwitz@potteranderson.com; ntarantino@Potteranderson.com; mbaker@potteranderson.com
Subject: Re:

Ken -- Can you at least tell us who Orchid India's designated agent is?

Jack

----- Original Message -----
From: KENNETH.SCHULER@lw.com <KENNETH.SCHULER@lw.com>
To: Blumenfeld, Jack; DMoore@potteranderson.com <DMoore@potteranderson.com>
Cc: RHorwitz@potteranderson.com <RHorwitz@potteranderson.com>; ntarantino@Potteranderson.com <ntarantino@Potteranderson.com>; mbaker@potteranderson.com <mbaker@potteranderson.com>
Sent: Thu Jan 31 17:31:54 2008

Subject: RE:

No. I don't think we agree that the notice letter is defective in any way, nor do I think that issue is relevant for present purposes. We are willing to accept service of the complaint as a courtesy to avoid any question as to whether service on Orchid Chemicals & Pharmaceuticals has been (or will be) accomplished in the lawsuit.

From: Blumenfeld, Jack [mailto:JBlumenfeld@MNAT.com]
Sent: Thursday, January 31, 2008 4:25 PM
To: Schuler, Kenneth (CH); DMoore@potteranderson.com
Cc: RHorwitz@potteranderson.com; ntarantino@Potteranderson.com; mbaker@potteranderson.com
Subject: Re:

Ken -- Is Orchid India designating Latham & Watkins as its agent as required by the cited CFR provision?

Jack

----- Original Message -----
From: KENNETH.SCHULER@lw.com <KENNETH.SCHULER@lw.com>
To: Blumenfeld, Jack; dmoore@potteranderson.com <dmoore@potteranderson.com>
Cc: rhorwitz@Potteranderson.com <rhorwitz@Potteranderson.com>; ntarantino@Potteranderson.com <ntarantino@Potteranderson.com>; mbaker@potteranderson.com <mbaker@potteranderson.com>
Sent: Thu Jan 31 17:22:58 2008
Subject: RE:

Jack, as I said yesterday during our phone conversation, Latham & Watkins will accept service on behalf of Orchid Chemicals & Pharmaceuticals.

From: Blumenfeld, Jack [mailto:JBlumenfeld@MNAT.com]
Sent: Thursday, January 31, 2008 3:12 PM
To: Moore, David E.
Cc: Horwitz, Richard L.; Tarantino, Nicole M.; Baker, Melinda S.; Schuler, Kenneth (CH)
Subject: RE:

David -- As indicated in my earlier email to Ken Schuler, Orchid India did not designate an agent for service of process in its notice letter, as required by 21 CFR 314.95(c)(7). Is Orchid India designating its Delaware sub as its agent? We need to know who the designated agent is before signing off on the stip.

Jack

From: Moore, David E. [mailto:dmoore@potteranderson.com]
Sent: Thursday, January 31, 2008 3:09 PM
To: Blumenfeld, Jack
Cc: Horwitz, Richard L.; Tarantino, Nicole M.; Baker, Melinda S.
Subject:

Jack

Attached is a draft stip for the Orchid Defs. Please let me know if this is ok with you.

David E. Moore
Attorney at Law
1313 North Market Street
P.O. Box 951
Wilmington, DE 19899-0951
302 984 6147 Direct Dial
302 658 1192 Fax
dmoore@potteranderson.com <mailto:dmoore@potteranderson.com>
www.potteranderson.com <http://www.potteranderson.com/>

For more information please go to http://www.lw.com/docs/irs.pdf
****

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Latham & Watkins LLP

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